

REMARKS**Interview Request**

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment, if there are any remaining objections or rejections. Applicants request the Examiner call Applicants' representative, as noted below.

Status of Claims

Prior to this amendment, claims 1-19 were pending and claims 3-6 were withdrawn.

By way of this amendment, Applicants cancel claims 1, 3-6, and 10-16 and amend claims 2, 7, 8, and 9. Therefore, upon entry of this amendment claims 2, 7, 8, 9, and 17-19 will be pending and under consideration. No new matter has been added by way of this amendment.

Amendments to Claims

The limitations of claim 1 have been added to the language of claim 2. In addition, claim 2 has been amended to recite specific crotonyl CoA reductases and isobutyryl CoA mutases that are either described in the specification and/or were known to one of skill in the art at the time of the invention.

Support for the amendments to claim 1 can be found, for example, at page 11, lines 27-29; page 12, lines 10-11; page 42, lines 3-5; page 57, lines 8-30; page 58, lines 6-7; page 70, lines 25-29; page 71, lines 17-19; and page 80, lines 7-13 and 16-23.

To illustrate that the biological sequences used in the claimed invention were known at the time of the invention, Applicants herein provide GenBank accession numbers for the sequences:

Claim Element	GenBank Reference accession no.
<i>icm</i> from <i>S. cinnamonesis</i>	U67612 (3/31/1998)
<i>ccr</i> from <i>S. collinus</i>	U37135 (3/27/1996)
<i>ccr</i> from <i>S. fradiae</i>	X81885 (6/21/1999)
<i>ccr</i> from <i>S. cinnamonesis</i>	AF178673 (8/18/99)
<i>ccr</i> from <i>S. coelicolor</i>	AL035161 (1/8/1999)

The following references provide further support for the amendments to claim 1 showing that the structure of various *icm* and *ccr* genes were known to one of skill in the art at the time of the invention. References 1-5 appear on page 80, lines 7-13 and 16-23 of the specification. Copies of the seven references are attached hereto.

1. Wallace, K. K., *et al.*, "Purification of crotonyl-CoA reductase from *Streptomyces collinus* and cloning, sequencing and expression of the corresponding gene in *Escherichia coli*," Eur. J. Biochem., 233:954-962 (1995).
2. Stassi, D. L., *et al.*, "Ethyl-substituted erythromycin derivatives produced by directed metabolic engineering," Proc. Natl. Acad. Sci. USA, 95:7305-7309 (1998).
3. Bate, N., *et al.*, "Multiple regulatory genes in the tylisin biosynthetic cluster of *Streptomyces fradiae*," Chem. Biol., 6:617-624 (1999).
4. Zerbe-Burkhardt, K., *et al.*, "Cloning, sequencing, expression, and insertional inactivation of the gene for the large subunit of the coenzyme B12-dependent isobutyryl-CoA mutase from *Streptomyces cinnamonensis*," J. Biol. Chem., 273:6508-6517 (1998).
5. Ratnatilleke, A., *et al.*, "Cloning and sequencing of the coenzyme B12-binding domain of isobutyryl-CoA mutase from *Streptomyces cinnamonesis*. Reconstitution of mutase activity, and characterization of the recombinant enzyme produced in *Escherichia coli*," Journal of Biological Chemistry, 274:1-7 (1999).
6. Vrijbloed, J.W., *et al.*, "Insertional inactivation of methylmalonyl coenzyme A (CoA) mutase and isobutyryl-CoA mutase genes in *Streptomyces cinnamonensis*: Influence of polyketide antibiotic biosynthesis," Journal of Bacteriology, 181: 5600-5605 (1999).
7. Lui, H., *et al.*, "Role of crotonyl coenzyme A reductase in determining the ratio of polyketides monesin A and monesin B produced by *Streptomyces cinnamonesis*," J. of Bacteriology, 181(21):6806-6813.

Lastly, claims 7-9 have been amended to be dependent from claim 2.

CONCLUSION

The amendment places the case in condition for allowance, does not raise any issues of new matter, and does not present new issues requiring further consideration or search. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance is respectfully requested.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 300622004810. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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